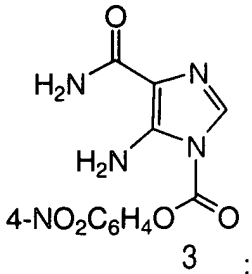
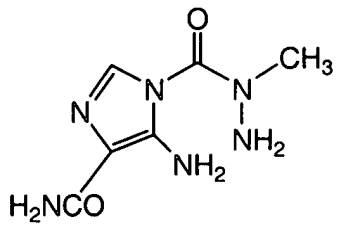


3 ;

b) reacting compound (3) with methylhydrazine in DMF at about 0°C to obtain compound (2):



(2) , and

c) reacting compound (2) with Bu_4NI in a 50/50 mixture of THF/CH_3CN, at a temperature of about (+) 60°C for a time of about 0 to about 60 minutes, followed by the cooling of the reaction mixture to about (+) 25°C and the addition of H_5IO_6 and stirring for about 10 to about 60 minutes to obtain temozolomide (1).

REMARKS

As an initial matter, applicant has submitted an Information Disclosure Statement, dated June 13, 2002, containing those references cited by the European Patent Office in the subject application's corresponding International PCT Application (PCT/US 02/01092). A copy of the IDS, PTO-1449 Form and PCT International Search Report dated May 24, 2002 are herein enclosed, as well as an authorization to charge Account No. 19-0365 for the Submission of IDS Fee of $180.00. Copies of the references have previously been provided to the Office, however, upon request, applicant will re-provide them to the Examiner. Applicant respectfully requests the entry of these references into the record.

Further, applicant has amended the specification to correct various typographical errors that appear within.

Claims 1-28 are pending in the application, all of which stand rejected for the reasons of record. Claims 4, 6, 7, 9, 10, 15, 21, 22 and 24 have been amended. No new matter has been added with the filing of this paper.

In view of the amendments and remarks that follow, applicant respectfully submits that the application is in condition for allowance. Accordingly, applicant requests reconsideration of the application, withdrawal of the rejections of record and issuance of a Notice of Allowance.

Allowable Subject Matter

Applicant gratefully acknowledges the Examiner's comments regarding the allowable subject matter. The Examiner stated that claims 26 and 28 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, to include all of the limitations of the base claim and any intervening claims. The Examiner stated said claims are allowable since specific species embrace in this claim are not taught or suggested by the art of record or from a search in the relevant art area.

Rejection Under 35 U.S.C. 112, second paragraph

Claims 1-26 stand rejected under 35 U.S.C. 112, second paragraph.

The Examiner stated that claim 1 is indefinite as it recites "a time sufficient enough to produce a compound of formula IA." The Examiner stated the term "sufficient time" is indefinite.

In response, applicant respectfully cites MPEP 2173.05(b), which, states that, the acceptability of relative terminology "claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification." Applicant believes that one of ordinary skill in the art would understand the relative time terminology of claim 1 to mean that period of time sufficient to produce a compound of formula IA. Accordingly, applicant respectfully submits that in view of the above argument, this ground of rejection should be withdrawn.

The Examiner stated that claim 3 in indefinite as to the definition of Z which is recited as "H, Hal."

In response, applicant respectfully refers the Examiner to page 8, lines 7-8 of the specification wherein Z is defined. Applicant respectfully notes that H represents hydrogen and "Hal" is halogen, which can be chlorine, bromine or iodine per page 8 of the specification. Accordingly, applicant respectfully requests the withdrawal of this rejection.

The Examiner stated that claim 5 recites the limitation of "KI" in line 2 of the claim. The Examiner stated there is insufficient antecedent basis for this limitation in the claims 4 or 5 on which claim 4 is dependent. The Examiner states that claim 4 does not recite KI.

In response, applicant has amended claim 4 to include as a source of iodide, an "inorganic iodide", of which KI is an example. Support for the amendment of claim 4 can be found on page 8, lines 15-17 of the specification. Therefore, amended claim 4 contains sufficient antecedent basis for the recitation of KI in claim 5. Accordingly, applicant respectfully requests the withdrawal of this rejection.

The Examiner stated that in claim 7, there is insufficient antecedent basis for the limitation of "toluene" in claim 7, or in claim 6 on which claim 7 is dependent upon.

In response, applicant has amended claim 7 to remove "toluene". Applicant has amended claim 6 to include toluene as an inert organic solvents listed therein. Support for this amendment can be found on page 8, lines 18-23, where toluene is listed as an example of an inert organic solvent. Accordingly, applicant respectfully requests the withdrawal of this rejection.

The Examiner stated that claims 8 and 9 are inconsistent in the recitation of temperatures as claim 8 has "+" and "-" before the numbers while claim 9 does not.

In response, applicant has amended claim 9 to read as "(+)60°C" so as to be consistent with claim 8. Accordingly, applicant respectfully requests the withdrawal of this rejection.

The Examiner stated that in claims 13 and 14, there is insufficient antecedent basis for the limitation of "acid binding agent" in said claims, or in claim 10 upon which claims 13 and 14 are dependent.

In response, applicant has amended claim 10 to recite the presence of an acid binding agent for the claimed process. Support for this amendment of claim 10 can be found in the specification on page 10, lines 15-18. Accordingly, applicant respectfully requests the withdrawal of this rejection.

The Examiner stated claims 16-22 are indefinite, as for example, claim 16 claims alkylhydrazine as a reactant while claims 21 and 22 use the same phrase "alkylhydrazine" while referring to a hydrazide.

In response, applicant has amended claims 21 and 22 by deleting the term "hydrazine" and inserting the language "said compound of formula II." Support for the amendment of claims 21 and 22 can be found on page 6, line 20 through page 7, line 1 of the specification. Accordingly, applicant respectfully requests the withdrawal of this rejection.

The Examiner stated claim 24 lacks consistency in its recitation of time ranges. In response, applicant has amended claim 24 to make said recited time ranges consistent with each other. Accordingly, applicant respectfully requests the withdrawal of this rejection.

Accordingly, applicant's respectfully submits that in view of the above claim amendments and argument, all the Examiner's rejections based on 35 U.S.C. Sec. 112, 2nd paragraph, should be withdrawn.

Rejection Under 35 U.S.C. 103

Claims 10, 23, 25 and 27 have been rejected under 35 U.S.C. Sec. 103 as being obvious over EPO 0113,570 (Chabala et al.). The Examiner stated that Chabala et al. teach several 5-amino-imidiazole compounds, in particular the compound of the formula found on page 2, wherein R^1 corresponds to the instant group bearing X on the imidazole nitrogens. The Examiner stated the instant claims differ from Chabala et al. in requiring specific protecting groups. The Examiner stated that Chabala et al. teaches the equivalency of exemplified R^1 groups in pages 11-28 of the reference with those of page 2. The Examiner states that it would have

been obvious to one of ordinary skill in the art to "make compounds variously substituted in the imidazole ring including various R^1 groups as permitted by the reference and expect resulting compounds to possess the uses taught by the art in view of the equivalency teaching outline above."

Applicant respectfully traverses the rejection and presents the following comments.

Applicant respectfully suggests that a *prima facie* case of obviousness cannot be established in light of Chabala et al. Per Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966) and MPEP § 2144, the criteria for a prima facie case of obviousness are:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence in the application indicating obviousness or nonobviousness.

Applicant notes the Examiner's acknowledgement of the differences between applicant's invention and the cited reference Chabala et al., specifically where the Examiner stated that the "instant claims differ from Chabala et al. in requiring specific protecting groups." Therefore, the scope of the Chabala et al. is not within scope of the claims of the present invention. This difference in scope precludes a finding of *prima facie* obviousness. Applicant respectfully suggests that these differences between the art and applicant's invention, per the first and second factors of Graham, a *prima facie* case of obviousness. Accordingly, applicant's respectfully submits that in view of the above argument, this ground of rejection should be withdrawn.

In view of the foregoing, applicant submits that the application, as amended, is in condition for allowance and courteously solicit a Notice of Allowance.

No fees, other than the $180.00 fee to submit an IDS, are believed to be due with this amendment. If any fees are determined to be due by this paper, the Commissioner is hereby authorized to deduct such fees from Account No. 19-0365.

PATENT CASE: **CD01352**
Serial No.: **10/050,768**
Filed: **January 16, 2002**

The Examiner is requested to call the undersigned attorney on any matter connected with this application.

Respectfully submitted,

William Lee
Reg. No. 46,100
Attorney for Applicant(s)
(908) 298-2161

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, D.C. 20231 ON 9/6/2002

William Lee
(REGISTERED REPRESENTATIVE)

9/6/2002
(SIGNATURE AND DATE)

PATENT CASE: **CD01352**
Serial No.: **10/050,768**
Filed: **January 16, 2002**

Version of Claims with Markings in Bold (Text to be deleted in brackets, t xt to be added underlined)

In the specification:

Please amend the specification as follows:

(Amended, Page 8 of specification lines 3-17) The oxidizing/cyclizing agent may be, for example, periodic acid (H_5I**[0]**O_6), iodine/potassium iodate, bromine or chlorine, or a reagent that oxidizes NH_2 to NZ, where Z represents **[0]**oxygen, (H,Hal), or Hal_2, wherein Hal is halogen and wherein the halogen is chlorine, bromine or iodine. Other suitable oxidizing agents include KI/KIO_3, I_2, I_2/KI**[0]**O_3, ICl, ICl_3, I_2**[0]**O_5, NCS/Me_2S, NBS/Me_2S, DCC/DMSO/H_3P**[0]**O_4, peracetic acid, $VO(acac)_2$/**[0]**O_2, $VO(acac)_2$/t-BuOOH, V_2**[0]**O_5, Bu_4NI/O_2, and MnO_2. Preferably, the oxidizing agent is H_5I**[0]**O_6 and the reaction is preformed in the presence of an iodide that is soluble in the reaction medium, the medium being an inert organic solvent.

(Amended, page, 12, lines 21-23) The reaction mixture was stirred vigorously for 4 hours and then left to stand for 18 hours at room temperature. The precipitate was collected by vacuum filtration and washed with H_2**[0]**O (1.5 L) to afford the product (3) as a pale yellow solid (42 g, 0.144 mol).

(Amended, page 14, lines 4-5) H_5I**[0]**O_6 (1.14 g, 5 mmol) was added and the reaction mixture was stirred vigorously at room temperature for 1 hour.

In the claims:

Please amend the claims as follows:

4. (Amended) The process of claim 1 wherein said iodide is a quarternary ammonium iodide **or inorganic iodide** and said inert medium is an inert organic solvent.

6. (Amended) The process of claim 4 wherein said inert organic solvent is selected from the group consisting of:

a) an amide;

b) an acyclic ether;

c) a cyclic ether;

d) an alkyl alkanoate wherein the alkyl group has 1 to 4 carbon atoms and the alkanoate **[grup]** **group** has 2 to 4 carbon atoms;

e) a halogenated hydrocarbon**;** **[and]**

f) toluene; and

[f)](g) mixtures thereof.

7. (Amended) The process of claim 6 wherein the organic solvent is selected from the group consisting of:

a) DMF;

b) t-butyl-methyl ether;

c) THF;

d) acetonitrile;

e) methylene chloride; **and**

f) **[toluene; and]**

[g)] mixtures of the above solvents**[,].**

9. (Amended) The process of claim 6 wherein:

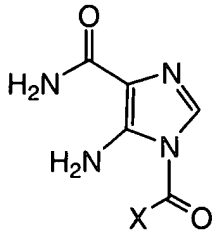
a) the organic solvent is a 50/50 mixture of THF/CH_3CN;

b) the oxidation/cyclization agent is H_5IO_6;

c) the iodide is Bu_4NI and

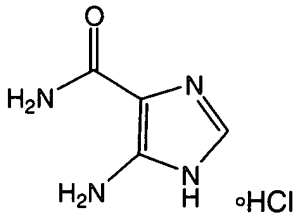
d) the reaction takes place at a temperature of about 0°C to about **(+)**60°C.

10. (Amended) A process for preparing a compound of the formula III:



III

which comprises reacting a compound of the formula 4:



4

with a compound of the formula X-CO-Y **in the presence of an acid binding agent**, wherein each of X and Y is the same or different leaving group, to yield a compound of the formula III.

15. (Amended) The process of claim 13 wherein the organic solvent is selected from the group consisting of

a) an amide;

b) an acyclic ether;

c) a cyclic ether;

d) an alkyl alkanoate wherein the alkyl group has 1 to 4 carbon atoms and the alkanoate **[grup] group** has 2 to 4 carbon atoms;

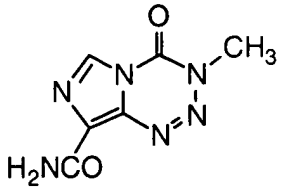
e) a halogenated hydrocarbon, and

f) mixtures thereof.

21. (Amended) The process of claim 17 wherein said **[alkylhydrazine] compound of formula II** is a 1-alkyl derivative of 5-amino-4-(aminocarbonyl)-1H-imidazole-1-carboxylic acid hydrazide wherein the alkyl group contains 1 to 6 carbon atoms.

22. (Amended) The process of claim 21 wherein said **[alkylhydrazin]** **compound of formula II** is 5-amino-4-(aminocarbonyl)-1H-imidazole-1-carboxylic acid 1-methylhydrazide.

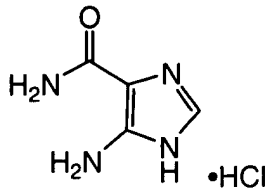
24. (Amended) A process for preparing temozolomide (1):



(1)

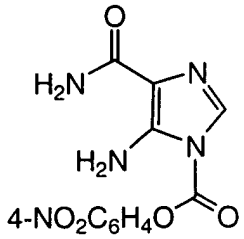
comprising:

a) reacting compound 4:



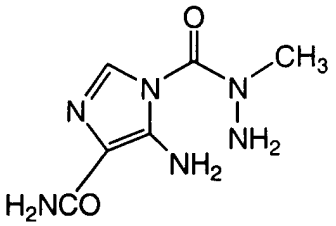
(4)

with 4-nitrophenyl chloroformate in the presence of triethylamine in CH_2Cl_2, under a nitrogen atmosphere at about 25°C to obtain compound (3):



3 ;

b) reacting compound (3) with methylhydrazine in DMF at about 0°C to obtain compound (2):



(2) , and

c) reacting compound (2) with Bu_4NI in a 50/50 mixture of THF/CH_3CN, at a temperature of about (+) 60°C for a time of about **[zero]0** to **[sixty]about 60** minutes, followed by the cooling of the reaction mixture to about (+) 25°C and the addition of H_5IO_6 and stirring for about 10 to about 60 minutes to obtain temozolomide (1).